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Contribution of Major Cardiovascular Risk Factors to Familial Premature Coronary Artery Disease

The GENECARD Project

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OBJECTIVES This study was designed to assess the prevalence of major cardiovascular risk factors in familial premature coronary artery disease (P-CAD), affecting two or more siblings within one sibship.

BACKGROUND Premature CAD has a genetic component. It remains to be established whether familial P-CAD is due to genes acting independently from major cardiovascular risk factors.

METHODS We recruited 213 P-CAD survivors from 103 sibships diagnosed before age ≤50 (men) or ≤55 (women) years old. Hypertension, hypercholesterolemia, obesity, and smoking were documented at the time of the event in 163 patients (145 men and 18 women). Each patient was compared with two individuals of the same age and gender, diagnosed with sporadic (nonfamilial) P-CAD, and three individuals randomly sampled from the general population.

RESULTS Compared with the general population, patients with sporadic P-CAD had a higher prevalence of hypertension (29% vs. 14%, $p < 0.001$), hypercholesterolemia (54% vs. 33%, $p < 0.001$), obesity (20% vs. 13%, $p < 0.01$), and smoking (76% vs. 39%, $p < 0.001$). These risk factors were equally or even more prevalent in patients with familial P-CAD (43% [$p < 0.05$ vs. sporadic P-CAD], 58% [$p = 0.07$], 21% and 72%, respectively). Overall, only 7 (4%) of 163 of patients with familial P-CAD and 22 (7%) of 326 of patients with sporadic P-CAD had none of these conditions, as compared with 167 (34%) of 489 patients in the general population.

CONCLUSIONS Classic, remediable risk factors are highly prevalent in patients with familial P-CAD. Accordingly, a major contribution of genes acting in the absence of these risk factors is unlikely. (J Am Coll Cardiol 2002;40:676–84) © 2002 by the American College of Cardiology Foundation

Coronary artery disease (CAD) has a familial component (1). Moreover, twin studies indicate that CAD is partly genetic and that the genetic contribution to CAD is more pronounced in premature forms of CAD (P-CAD) (2). However, Mendelian-dominant atherogenic disorders, such as familial hypercholesterolemia, account for only a small fraction of P-CAD (<5%) (3), indicating that the genetic basis of P-CAD is, in most cases, complex. As such, the molecular genetic basis of P-CAD remains to be elucidated.

Affected sibling-pair analyses are being increasingly used to explore the genetic basis of complex diseases like P-CAD (4). In this type of analysis, whole-genome scanning is performed on large numbers of affected sibling pairs, and genomic regions that are shared in excess between affected siblings are subsequently screened for the presence of specific sequence variants associated with the disease. Whether causative genetic defects suffice to trigger the development of familial forms of P-CAD independently from classic risk factors, such as lipid disorders, hypertension and cigarette smoking, is a major issue that has profound implications for predictive and preventive medicine, as well as for research endeavors, and that has not been fully documented yet.

A variety of convergent observations suggest that independent genetic defects may be at work in familial forms of P-CAD. A positive family history of P-CAD has been repeatedly reported as an independent cardiovascular risk factor (5,6). Next, atherosclerotic carotid plaques (7), defects in myocardial perfusion (8), endothelial dysfunction (9) and electrocardiographic abnormalities (10) have been recently detected in apparently healthy first-degree relatives of patients with P-CAD, and these associations have been shown to persist after adjustment for classic cardiovascular risk factors. In contrast, first-degree relatives of patients with P-CAD have also been shown to present with an

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Abbreviations and Acronyms

CAD	= coronary artery disease
CI	= confidence interval
HDL	= high-density lipoprotein
OR	= odds ratio
P-CAD	= premature coronary artery disease

elevated prevalence of metabolic abnormalities (11)—in particular, hyperlipidemia (3,12), small, dense low-density lipoprotein particles (13), and hypertension (14)—suggesting that P-CAD in affected sibling pairs may be, at least in part, mediated by a familial, possibly genetic predisposition to these intermediate traits.

In the present study, we envisioned three scenarios to account for the development of familial P-CAD. In the first scenario, we reasoned that if familial P-CAD was due to genetic defects acting independently from "traditional," major cardiovascular risk factors, one should observe a prevalence of these risk factors in P-CAD–affected sibling pairs lesser than or similar to the prevalence in the general population and lesser than that in patients with sporadic (i.e., nonfamilial) P-CAD, who may not carry such a genetic predisposition. In the second scenario, P-CAD in affected sibling pairs may be a consequence of genetic defects leading to atherogenic metabolic disorders—the paradigm here being familial hypercholesterolemia. If this scenario is correct, one should observe a very high prevalence of metabolic disorders in P-CAD–affected sibling pairs (even higher than that in patients with sporadic P-CAD), a certain concordance for these intermediate traits in P-CAD–affected siblings from the same sibship and a prevalence of smoking equivalent to that in the general population. Finally, in the third scenario, where P-CAD in affected sibling pairs was due to a genetic predisposition to metabolic disorders acting in concert with specific environmental conditions like smoking, one would expect a prevalence of atherogenic metabolic disorders and smoking similar to that in patients with familial and sporadic P-CAD and higher than that in the general population.

To explore which of these scenarios is at work in familial P-CAD, we examined the prevalence of hypertension, hypercholesterolemia, obesity, and cigarette smoking in a unique group of 213 P-CAD survivors from 103 Caucasian sibships with two or more affected siblings, recruited in Western Switzerland within the framework of the GENECARD project, a multinational effort to elucidate the genetic basis of CAD using an affected sibling-pair approach. We compared these patients with familial P-CAD with age- and gender-matched individuals randomly sampled from the general population within the framework of the Swiss MONICA project and with patients diagnosed locally with sporadic (nonfamilial) P-CAD.

METHODS

Study design and recruitment of patients with familial P-CAD. In the GENECARD project, which will be described in detail separately (W.E. Krauss et al., manuscript in preparation), P-CAD is defined by the presence of acute myocardial infarction or angina with ≥50% stenosis within a major coronary vessel on the angiogram, diagnosed before age ≤50 years for men and ≤55 years for women. To be included in the GENECARD study, P-CAD survivors had to have at least one sibling who had equally survived P-CAD. Cocaine users, patients with end-stage renal disease and individuals who had previously undergone radiotherapy of the chest were excluded from the study.

To identify P-CAD–affected sibling pairs, we initially screened the medical records of >35,000 patients who had been admitted for heart disease between 1985 and 2000 to our University Hospital and to four major public hospitals and two large rehabilitation centers in Western Switzerland (listed in the Appendix), covering a population of ~1.2 million residents (Fig. 1). A total of 4,255 individuals (100%) who had been diagnosed with P-CAD were identified. A letter describing the aim of the GENECARD project was sent to 3,075 patients (72%); the remaining 1,180 patients (28%) were deceased or could not be located. A total of 1,795 individuals (42%) responded to the letter and provided a detailed history of CAD in their family. A second letter was sent to responders who reported at least one potentially eligible sibling; this letter asked for permission to contact the sibling. Potentially eligible siblings were informed regarding the project and were asked for permission to examine their medical records. A total of 110 individuals (2.7%) with at least one sibling who had equally survived P-CAD were identified after the presence of the disease had been fully verified for all affected siblings in the original documents. Seven individuals from separate sibships refused to enter the study, so a total of 213 individuals from 97 sibships with two P-CAD–affected siblings, five sibships with three P-CAD–affected siblings, and one sibship with four P-CAD–affected siblings were eventually recruited. These individuals (all Caucasians) comprised the familial P-CAD group. The procedures were in accordance with institutional guidelines and the Swiss Office for Patients' Protection. The protocol was approved by the local ethics committees, and each participant provided written, informed consent.

Major risk-factor profile at the time of the event. Medical charts recorded at the time that the diagnosis of P-CAD was initially made were retrieved for these 213 patients with familial P-CAD. A description of smoking and hypertension and measurements of body mass index and plasma total cholesterol levels (if measurement was performed within 24 h of the initiation of symptoms or at least after 12 weeks for subjects diagnosed with acute myocardial infarction) were documented for 163 subjects diagnosed before age ≤50 years (30 subjects for whom the complete

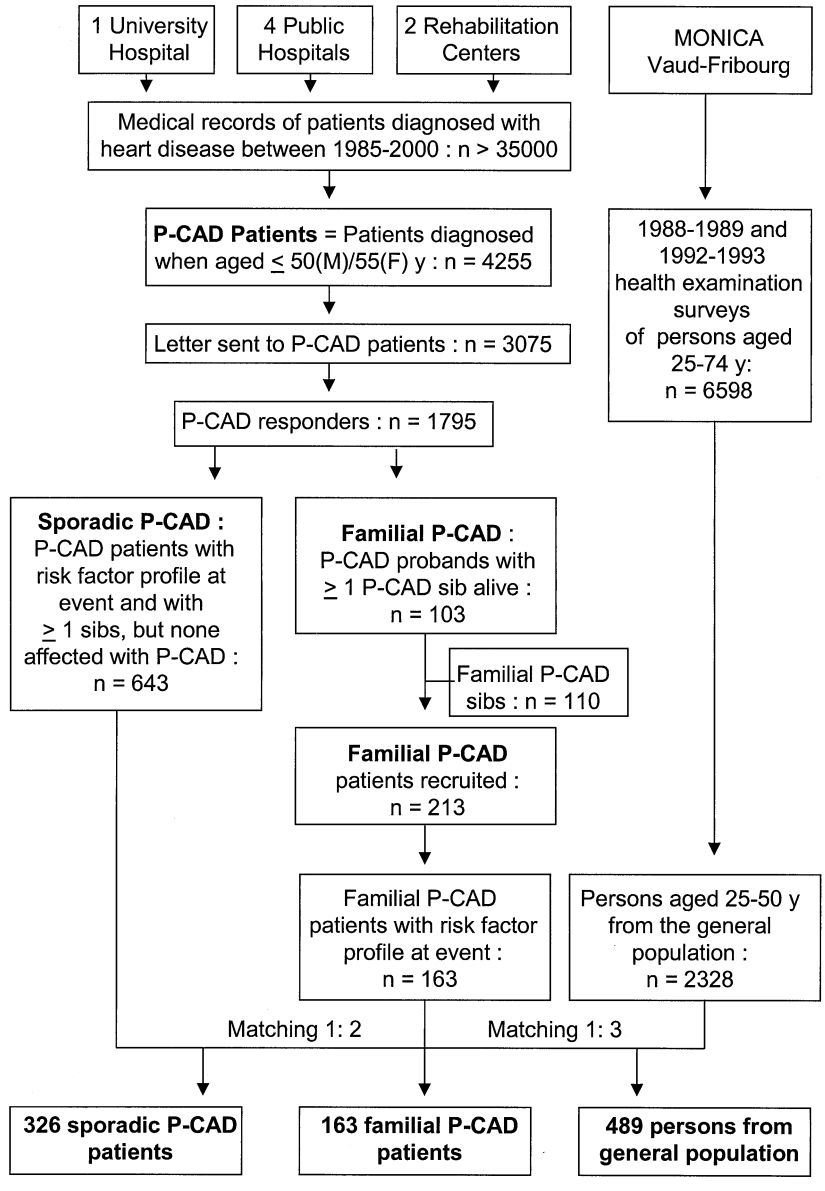

Figure 1. Strategy used to recruit premature coronary artery disease (P-CAD)–affected sibling pairs and to identify patients with sporadic P-CAD. A total of 110 patients with familial P-CAD were originally identified, but 7 refused to enter the study, so that 103 probands with familial P-CAD and 110 affected siblings were eventually recruited.

risk-factor profile was not properly documented and 20 women diagnosed between age 51 and 55 years were excluded from this analysis), including 128 individuals from 64 sibships. In this analysis, hypertension was defined as blood pressure ≥160/95 mm Hg or prescription of antihypertensive agents; hypercholesterolemia as plasma total cholesterol levels ≥6.5 mmol/l or prescription of lipid-lowering agents; obesity as a body mass index ≥30 kg/m^2; and smoking as active cigarette smoking at the time of the event or within the five preceding years. Plasma high-density lipoprotein (HDL) cholesterol levels were only available for 87 patients with familial P-CAD, and this variable was not included in the analysis.

Identification of the sporadic P-CAD group. Patients with familial P-CAD were compared with patients with sporadic (nonfamilial) P-CAD. To identify these patients with sporadic P-CAD, we selected, out of a group of 1,172 individuals who had been admitted to our University Hospital for P-CAD and for whom a complete risk-factor profile was recorded at the time of the event, 838 patients who had responded to our letter. A total of 80 patients who had no sibling and 115 patients who reported to have one or more siblings affected with CAD (irrespective of age) were excluded from the group, so that 643 patients with P-CAD who had at least one sibling, but none reported to be affected with CAD, were eventually included in the sporadic P-CAD group (Fig. 1).

General population matching procedure and statistical analysis. Each of the 163 patients with familial P-CAD was randomly matched to two patients with sporadic

Table 1. Clinical Characteristics of Patients With Familial P-CAD at the Time of the Event and Their Matched Control Subjects

	General Population (n = 489)	Sporadic P-CAD Group (n = 326)	Familial P-CAD Group (n = 163)
Gender (M/F)	435/54	290/36	145/18
Age (yrs)	44.0 ± 4.6	44.0 ± 4.5	44.0 ± 4.6
Diagnosis of MI/angina	—	195/131	82/81
TC (mmol/l)	6.4 ± 1.3	6.4 ± 1.5	6.5 ± 1.5
Hypercholesterolemia (TC ≥6.5 mmol/l)	33%	54%*	58%*
HDL cholesterol (mmol/l)	1.27 ± 0.35	1.09 ± 0.50*	1.02 ± 0.29*†
BMI (kg/m^2)	26.0 ± 3.6	26.9 ± 3.9	27.2 ± 3.9
Obesity (BMI ≥30 kg/m^2)	13%	20%*	21%*
Hypertension	14%	29%*	43%*
Smoking	39%	76%*	72%*
Diabetes	‡	7.7%	9.2%

*$p < 0.001$ versus general population. †Plasma HDL cholesterol levels were available for 87 patients with familial P-CAD, and a comparison was made with 174 age- and gender-matched patients with sporadic P-CAD and 261 age- and gender-matched subjects from the general population. ‡The presence of diabetes was not recorded in the MONICA surveys, so these data are missing. In the U.K. and other European countries, the prevalence of diabetes in Caucasians aged <50 years from the general population appears to be <1.0%. Data are presented as the number or percentage of patients or the mean value ± SD.

BMI = body mass index; HDL = high-density lipoprotein; MI = myocardial infarction; P-CAD = premature coronary artery disease; TC = total cholesterol.

P-CAD of the same gender and age. In addition, each patient was randomly matched to three individuals of the same gender and age, among 2,328 individuals aged 25 to 50 years who participated in two population-based health examination surveys conducted in Western Switzerland (Cantons of Vaud and Fribourg) in the periods 1988–1889 and 1992–1993 within the framework of the Swiss MONICA project (15). An allowance for a small difference in age (maximum of 3 years) was introduced in the matching criteria to achieve a fixed case-control ratio of 1:2 (for patients with sporadic P-CAD) or 1:3 (for individuals from the general population). Conditional logistic regression for case-control studies (16) was used to calculate the odds ratios (ORs) and their confidence intervals (CIs) for the various cardiovascular risk factors. Statistical analyses were carried out using STATA (release 6.0, STATA Corp., College Station, Texas) and SPSS (release 4.0, SPSS, Inc., Chicago, Illinois).

RESULTS

We locally recruited 213 Caucasian P-CAD survivors (175 men and 38 women) from 103 sibships, with fully verified P-CAD in the original documents (Fig. 1). Two sibships (2%) fulfilled the clinical criteria for familial hypercholesterolemia (17). About half of the sibships for whom reliable information was available (38 [48%] of 79) reported a positive parental history of CAD, as defined by CAD in either or both parents diagnosed before age ≤60 years for fathers or ≤65 years for mothers; the remaining 24 families

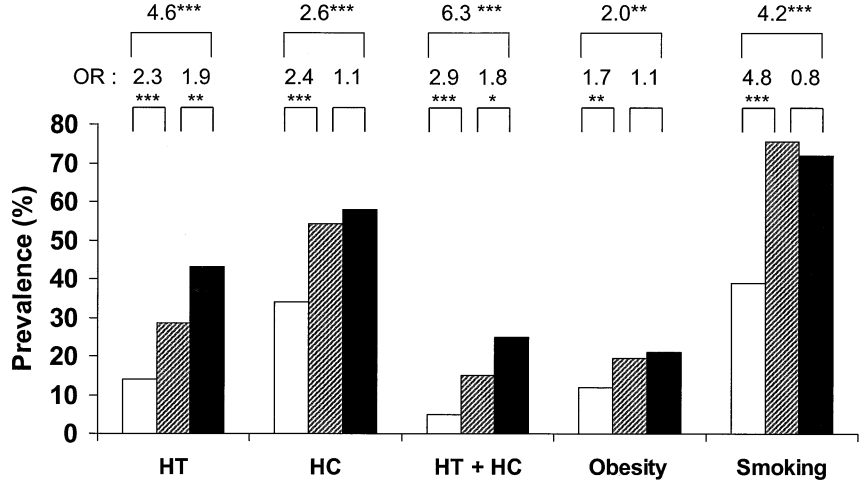

Figure 2. The prevalence of hypertension (HT), hypercholesterolemia (HC), obesity and cigarette smoking at the time of the event in 163 patients with familial premature coronary artery disease (P-CAD) **(solid bars)**, 326 age- and gender-matched patients with sporadic (nonfamilial) P-CAD **(hatched bars)** and 489 age- and gender-matched individuals randomly sampled from the local general population **(open bars)**. Hypertension was defined as blood pressure ≥160/95 mm Hg and/or prescription of antihypertensive agents; hypercholesterolemia corresponded to plasma total cholesterol levels ≥6.5 mmol/l and/or prescription of lipid-lowering agents; obesity was defined as a body mass index ≥30 kg/m^2; and smoking corresponded to active cigarette smoking at the time of diagnosis or within the preceding five years. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

were not included in this analysis due to an unknown condition or death from noncardiac origin of either or both parents before age ≤60 years for men and ≤65 for women years.

The major cardiovascular risk-factor profile (hypertension, hypercholesterolemia, obesity and smoking) at the time of the event was documented for 163 P-CAD–affected siblings (145 men and 18 women) diagnosed before age ≤50 years (Table 1), and the profile in these patients with familial P-CAD was compared with that of 326 age- and gender-matched patients with sporadic (nonfamilial) P-CAD and 489 age- and gender-matched individuals randomly sampled from the local general population (Fig. 1). The presence of diabetes was documented in patients with familial P-CAD (9.2%) and in matched persons with sporadic P-CAD (7.7%), but was not documented in the MONICA participants, so this variable was not included in the analysis. Plasma total cholesterol levels were similar in the three groups; however, a higher proportion of individuals receiving lipid-lowering agents was observed in the two P-CAD groups compared with the general population (15% and 9% vs. 2%). In contrast, plasma HDL cholesterol levels were lower in both P-CAD groups than in the general population ($p < 0.001$). Overall, when compared with patients with sporadic P-CAD, patients with familial P-CAD presented with an equally elevated or even higher prevalence of hypertension, hypercholesterolemia, combination of hypertension and hypercholesterolemia, obesity, and smoking (Fig. 2). These risk factors were approximately twice as prevalent in patients with sporadic P-CAD than in the general population. Similar results were obtained when comparing men with familial P-CAD with patients with sporadic P-CAD sharing the same age and parental history of CAD.

Next, we examined the intra-individual sum of major risk factors within each group. Only a small fraction of patients with familial or sporadic P-CAD (7 [4%] of 163 and 22 [7%] of 326, respectively) had none of these conditions, as compared with 167 (34%) of 489 subjects in the general population. On average, patients with familial P-CAD presented with 1.9 ± 0.9 risk factors, as compared with 1.8 ± 0.9 risk factors in patients with sporadic P-CAD ($p = 0.06$) and 1.0 ± 0.9 risk factors in the general population ($p < 0.001$).

The prevalence of major risk factors varied according to age (Fig. 3). Compared with the general population, the prevalence of hypertension, hypercholesterolemia, obesity, and smoking was higher in both P-CAD groups at all age tertiles. No difference was observed between familial and sporadic patients with P-CAD in the younger age tertile (27 to 42 years; n = 53 and 106, respectively). In contrast, in the third age tertile (47 to 50 years), patients with familial versus sporadic P-CAD (n = 56 and 112) had a higher prevalence of hypertension (OR 3.1 [95% CI 1.6 to 6.2], $p = 0.001$), alone or in combination with hypercholesterolemia (OR 2.4 [95% CI 1.1 to 5.3], $p = 0.02$), than did patients with sporadic P-CAD. Overall, the sum of risk factors in this third age tertile was higher in patients with familial versus sporadic P-CAD (2.1 ± 0.8 vs. 1.8 ± 0.9, $p = 0.05$).

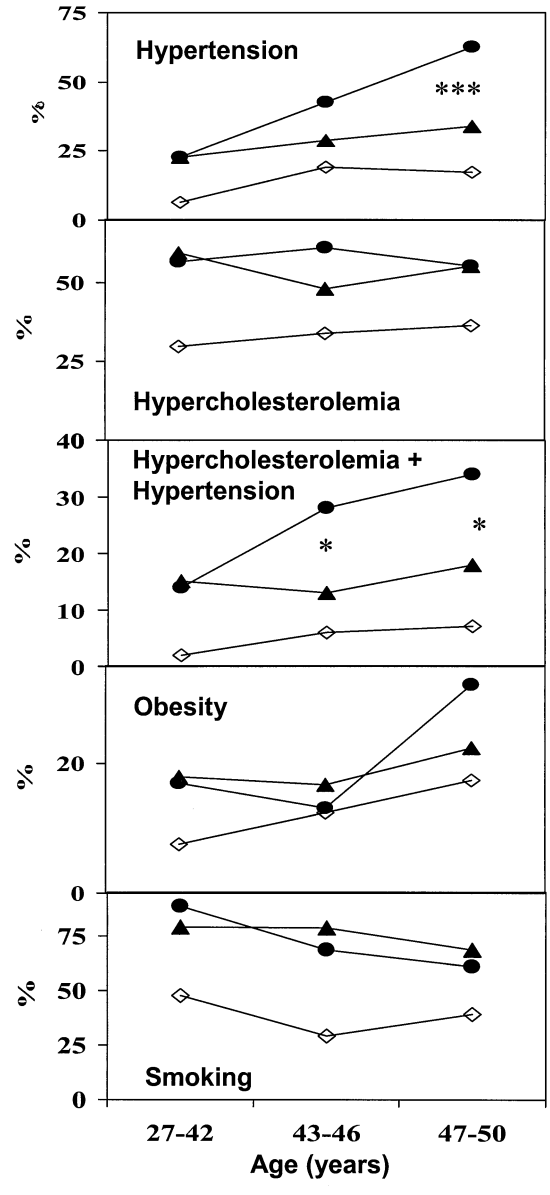

Figure 3. The prevalence of risk factors in the general population **(open diamonds)**, in patients with sporadic premature coronary artery disease (P-CAD) **(solid triangles)** and in patients with familial P-CAD **(solid circles)**, according to age tertiles. Groups and risk factors were defined as described in the legend to Figure 2. *$p < 0.05$ familial versus sporadic P-CAD; ***$p < 0.001$.

The difference in the prevalence rate of hypertension and hypercholesterolemia between patients with familial and those with sporadic P-CAD was particularly pronounced for the subset of patients with familial P-CAD with a positive parental history of CAD (Table 2). Hypertension was equally prevalent in the sporadic and familial P-CAD groups when considering patients with familial P-CAD with a negative parental history of CAD (35% vs. 31%, p =

Table 2. Prevalence Rates of Major Cardiovascular Risk Factors in Patients With Familial P-CAD and Their Respective Age- and Gender-Matched Control Subjects, According to Parental History of CAD in Patients with Familial P-CAD*

	Prevalence (%)			OR (95% CI)		
	General Population (A)	Sporadic P-CAD Group (B)	Familial P-CAD Group (C)	B vs. A	C vs. B	C vs. A
Negative (n)	177	118	59			
Positive (n)	192	128	64			
HT						
Negative	18%	31%	35%	2.0 (1.1–3.4)	1.3 (0.6–2.5)	2.5 (1.3–4.7)
Positive	11%	29%	53%	3.1 (1.8–5.6)	2.7 (1.4–5.2)	13.1 (5.4–31.6)
HC						
Negative	33%	49%	54%	2.2 (1.4–3.7)	1.2 (0.7–2.3)	2.3 (1.3–4.1)
Positive	33%	66%	62%	3.3 (2.1–5.2)	0.9 (0.5–1.6)	3.2 (1.8–5.7)
HT + HC						
Negative	5%	15%	24%	2.6 (1.2–5.6)	1.7 (0.8–3.7)	3.5 (1.6–7.8)
Positive	4%	17%	30%	3.4 (1.6–7.2)	1.9 (0.9–3.8)	8.3 (3.5–19.7)
Obesity						
Negative	15%	18%	24%	1.3 (0.7–2.5)	1.4 (0.7–3.0)	2.0 (0.9–4.4)
Positive	10%	21%	14%	2.5 (1.3–4.8)	0.6 (0.3–1.4)	1.5 (0.6–3.5)
Smoking						
Negative	40%	76%	73%	5.4 (3.0–9.2)	0.8 (0.4–1.7)	4.7 (2.3–9.5)
Positive	37%	77%	77%	5.8 (3.4–9.7)	1.0 (0.5–2.0)	5.4 (2.8–10.3)

*Family history of coronary artery disease was defined as positive if one or both parents had been diagnosed with coronary artery disease at age ≤60 years for men and ≤65 years for women. This information was not available for 40 patients with familial P-CAD due to an unknown condition or death of noncardiac origin of the parent(s) before reaching this age.

CI = confidence interval; HC = hypercholesterolemia; HT = hypertension; OR = odds ratio; P-CAD = premature coronary artery disease.

NS). In contrast, the difference was very pronounced when examining patients with familial P-CAD with a positive versus negative parental history (53% vs. 29% and $p < 0.001$ vs. $p = 0.05$, respectively). This analysis suggested that hypertension runs in these families and contributed to CAD in both the parental generation and the sibling pairs recruited here.

To further explore the familial aggregation of risk factors in patients with familial P-CAD recruited here, we next examined the intra-sibling-pair concordance for these risk factors. The proportion of sibling pairs with both siblings being hypertensive was significantly higher than the proportion observed for their matched control subjects from the sporadic P-CAD group (26% vs. 9%, OR 3.3, $p = 0.004$) and the general population (3%, OR 12.3, $p < 0.001$). Similarly, the concordance for hypercholesterolemia was higher in familial P-CAD sibships than in the control subjects from the general population (33% vs. 22%, OR 2.0, $p = 0.03$), but not for obesity or smoking. Similar conclusions could be drawn when testing for concordance using the Kappa test (Table 3). In this analysis, the observed intra-sibling-pair concordance was higher than expected when assuming independence from hypertension (62.5% vs. 50.2%, $p = 0.02$) and hypercholesterolemia (62.5% vs. 49.7%, $p = 0.02$) between siblings, but not for obesity or for smoking. Finally, the high proportion of sibling pairs with two hypertensive siblings was mostly accounted for by those sibling pairs with a positive parental history of CAD (40% [n = 23] vs. 13% in sibling pairs with a negative parental history [n = 25], $p = 0.04$).

Six sibships were characterized by the presence of three or four P-CAD survivors, and these sibships are particularly illustrative of the findings reported earlier (Fig. 4). Only one of these six sibships (family no. 80) had a positive parental history of CAD diagnosed before age 60 years (for fathers) and 65 years (for mothers), and 9 of 12 parents survived into their 60s (note that in family no. 75, the father died at age 83 years and the mother was aged 86 years). None of the affected siblings had no risk factor, and all siblings had at least one metabolic risk factor (hypertension, hypercholesterolemia, or obesity and diabetes), except the younger sibling in family

Table 3. Number of Siblings With Major Cardiovascular Risk Factors in 64 Sibling Pairs* Affected With Familial Premature Coronary Artery Disease

	No. of Affected Siblings in Sibling Pair			Kappa Value
	0	1	2	
HT				
Observed	36	38	26	0.02
Expected†	30	50	20	
HC				
Observed	27	37	36	0.02
Expected†	20	50	30	
HT + HC				
Observed	59	32	9	0.09
Expected†	56	38	6	
Obesity				
Observed	57	38	5	0.64
Expected†	58	36	6	
Smoking				
Observed	9	39	52	0.30
Expected†	8	41	51	

*Information was missing for 40 sibling pairs. †Value obtained when assuming independence of risk-factor distribution among affected siblings from the same sibship.

HC = hypercholesterolemia; HT = hypertension.

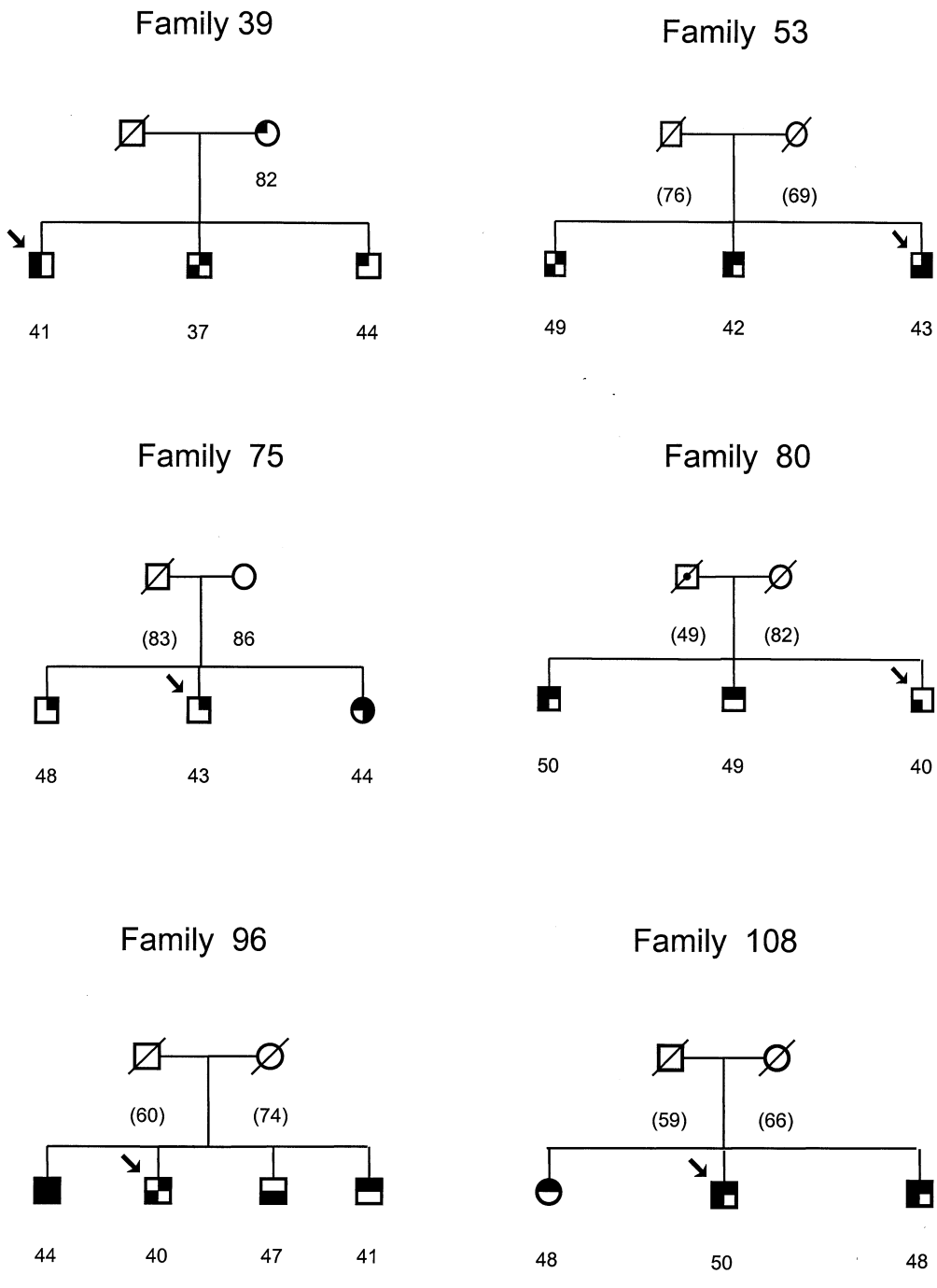

Figure 4. Aggregation of cardiovascular risk factors at the time of the event in six sibships with at least three siblings affected with premature coronary artery disease (P-CAD). Males are represented by **squares** and females by **circles**. The numbers beneath the symbols refer to the age when the diagnosis of P-CAD was made, whereas the age for the parents refers to the age at death (numbers in parentheses) or at the time that their P-CAD–affected siblings were recruited (age at death of the father for family no. 39 was unknown). **Solid upper left corner** = hypertension; **solid lower left corner** = smoking; **solid upper right corner** = hypercholesterolemia; and **solid lower right corner** = obesity and/or diabetes, as defined in the legend to Figure 2. **Arrows** indicate probands. Plasma cholesterol levels were missing for siblings 1 and 3 from family no. 53, sibling 1 from family no. 80 and sibling 1 from family no. 96, and the diagnosis of hypercholesterolemia was based on values obtained when these individuals were recruited. The father in family no. 80 died of P-CAD at age 49 years.

no. 80 who was diagnosed with P-CAD at age 40 years. When recruited at age 47 years, however, this person was obese and hypercholesterolemic. Hypertension tended to aggregate in siblings from four of six families (family nos. 39, 80, 96, and 108), whereas hypercholesterolemia affected at least two siblings in five of six families (except family no. 39).

DISCUSSION

The major finding of this study is that familial P-CAD is associated with a prevalence of hypertension, hypercholesterolemia, obesity, and cigarette smoking that was about twice as high as that in the general population and equally

high, if not higher, than that in patients with sporadic P-CAD. Moreover, hypertension and, to a lesser extent, hypercholesterolemia were associated with a parental history of CAD and tended to aggregate in sibling pairs recruited here. Finally, cigarette smoking was the most prevalent risk factor in both P-CAD groups. Taken together, these data illustrate the importance of hypertension and dyslipidemia, as well as life-style (particularly smoking), in the development of both familial and sporadic P-CAD.

Comparison with other studies and limitations of the present study. Only limited information is available on cardiovascular risk factors in P-CAD (18–20). The present study is based on a unique, ethnically and geographically homogeneous, large group of sibling pairs for whom P-CAD had been fully verified in the original documents and who had been carefully matched to local patients with sporadic P-CAD and individuals randomly sampled from the general population during the same period. Nevertheless, this study has its limitations. The prevalence, at the time of the event, of major risk factors in patients with P-CAD was based on a retrospective analysis of medical records. This approach was dictated by the extreme rarity of sibships with multiple P-CAD survivors in Western Switzerland (a region characterized by one of the lowest age-adjusted incidences of CAD in industrialized countries) (15,21) and the fact that a substantial proportion of participants had changed their profile after being diagnosed with P-CAD (for instance, 55% of those individuals who were smokers when initially diagnosed with P-CAD had quit smoking at the time they were recruited in the present study). Next, only survivors were included in the familial P-CAD group to be recruited into the GENECARD project; if the factors under study are related to both the risk of P-CAD and survival, this may introduce a confounding factor in the assessment of cardiovascular risk. For example, because diabetes both promotes the development of atherosclerosis and leads to a poorer outcome after myocardial infarction, this risk factor may be under-represented in the familial P-CAD group. Finally, a series of risk factors, such as HDL cholesterol levels, lipoprotein(a) or homocystinemia, could not be examined in the present study.

Despite these limitations, our present results on sporadic P-CAD are in very close agreement with autopsy studies on premature atherosclerosis (19), as well as prospective studies on P-CAD (18). In the Bogalusa Heart Study (19), the extent of atherosclerosis in young adults, assessed at autopsy, closely correlated to the number of cardiovascular risk factors, whereas in the Chicago Heart Association Detection Project in Industry Study (18), risk factors such as cholesterol levels in plasma, systolic blood pressure and cigarette smoking were highly predictive of death due to CAD in men aged 18 to 39 years. Finally, our data are in agreement with those of Williams et al. (20), who reported an elevated prevalence of lipid disorders in 44 patients with P-CAD from 33 families with two or more P-CAD–affected siblings.

Clinical implications. The elevated prevalence of major cardiovascular risk factors in patients with familial P-CAD is associated with a series of immediate implications for preventive medicine and genetic endeavors. From a clinical standpoint, lipid disorders, hypertension, and smoking are remediable risk factors. The absence of these conditions is associated with a very low incidence of heart disease and a longer life-expectancy in the general population (22), and there is no reason to believe that members of families heavily loaded with CAD will not benefit as much as the general population from interventions aimed at reducing these remediable risk factors. Given the familial aggregation of lipid disorders and hypertension in first-degree relatives of patients with P-CAD (11–13), the presence of these risk factors should be sought and treated vigorously in unaffected siblings and, possibly, in their offspring.

Implications for the genetics of CAD. The implications of the present study for genetic endeavors on CAD are not less important. The very high prevalence of smoking, hypertension and hyperlipidemia raises the question as to whether familial P-CAD in the patients recruited here is somehow genetic. The data provide part of the answer to this question. First, the elevated prevalence of hypertension and hypercholesterolemia among patients with familial P-CAD, the concordance for these traits in affected sibling pairs, and the association of hypertension with a positive parental history of CAD, all converge to support the presence of a familial, possibly genetic predisposition to these traits, which indirectly contributes to the development of P-CAD, at least in a subset of sibships. Next, genes may be at work in some patients to promote the development of P-CAD in the presence of major risk factors. The presence of such genes for CAD has recently been demonstrated for a particular sequence variant within the lipoprotein lipase gene *(D9N)*, which exclusively increases the risk for heart disease in smokers (23). Finally, the fact that patients with familial P-CAD had a risk-factor profile worse than that of patients with sporadic P-CAD in the third age tertile renders a major contribution of genes acting independently from well-known classic risk factors unlikely, at least in this age category. Taken together, our present data reinforce the need to more closely investigate the gene–environment interactions in genetic studies on CAD and to further explore the genetics of hypertension and hyperlipidemia.

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APPENDIX

Data were derived from the medical records of the following institutions: *CHUV University Hospital, Lausanne:* Peter Burckhardt (Department of Medicine), Lukas Kappenberger and Jean-Jacques Goy (Division of Cardiology), Ludwig von Segesser (Department of Cardiovascular Surgery) and Marie-Denise Schaller (Division of Intensive Care Unit); *Centre de Réhabilitation de Genolier:* Cédric Vuille; *Centre de Réhabilitation de la Lignière:* Claude-Alain Nacht; *Hôpital des Cadolles de Neuchâtel:* Rehza Kehtari; *Hôpital Cantonal de Fribourg:* Claude Regamey, Jean-Christophe Stauffer, Adrien Nicole, and Benoît Quarteno-ud; *Hôpital du Sud du Canton de Fribourg à Riaz:* Jean-Daniel Morard; and *Hôpital de la Ville de Sion:* Pierre Vogt and Christophe Imsand.